Remarks

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 34, and 41-45, were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 U.S.P.Q. 659 (C.C.P.A. 1976). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 13321, 1332 (Fed. Cir. 1991); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)).

Whether undue experimentation is needed is not based upon a single factor; it is a conclusion reached by weighing many factors. These factors have been summarized in *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and include, but are not limited to:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The relative skill of those in the art;

(7) The predictability or unpredictability of the art; and

(8) The breadth of the claims.

The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to each of these factors (see M.P.E.P. § 2164.01 (a)).

The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). In addition, the adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. See Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). **There is no requirement for examples.**

Claims 34, 41-44, and 46-47 are enabled.

Claim 34 has been amended to more clearly define a system as a "therapeutic system." Support for this amendment can be found in the specification at least at page 1, lines 3-5. Therapeutic systems in general are described in the specification at least at pages 1-3. Description of the therapeutic system as defined by the claims can be found in the specification at least at page 37, lines 13-17. Claim 42 has been amended to correct a clerical error. Support for this amendment can be found in the specification at least at page 51, lines 6-7. Claim 44 has been amended to depend from claim 42 since the "R" group is only present in formula II of claim 42. Claim 44 has also been amended to include $-CH_2CH_2OH$. Support for this amendment can be found in the specification at least at page 51, lines 10-22. Claim 45 has been canceled. Support for new claim 46 can be found in the specification at least at page 37, lines 19-20. Support for new claim 47 can be found in the specification at least at page 37, lines 19-20.

The specification discloses to one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. The claims as amended define a therapeutic system that contains **a prodrug that is converted to a substantially cytotoxic drug by the action of NQO2** and a compound of formula I. This functional wording places a clear limitation on the scope of the claims. Therefore, claim 34 does not include any and all prodrugs, but only those prodrugs which are converted to a substantially cytotoxic drug by the action of NQO2. The prodrugs as defined by the claims are those that are capable of interacting with NQO2 to form a cytotoxic species. It is clear that prodrugs that **cannot** be converted by NQO2 into a

cytotoxic species do not fall within the scope of the claims. Therefore, the claims as amended do not include any and all prodrugs, not the least because NQO2 is an example of the general class of reductases (see page 7, lines 26-27 of the specification), which will only interact with certain chemical functional groups to form cytotoxic species.

Prodrugs such as CB 1954 and analogues of CB 1954 that might be converted by the action of NQO2 are disclosed in the specification at least at page 37, lines 16-28, and page 38 lines 1-2, and lines 16-17. In addition, the specification at least at page 37, lines 22-26 provides a person with ordinary skill in the art a starting point for identifying suitable analogs of CB 1954. The mechanism shown in Figure 1 in the present application also provides guidance for identifying analogs of CB 1954 that can be converted by NQO2 into cytotoxic species. Therefore, the specification provides guidance as to the core functional groups and structures that provide activity, which can then be extrapolated to a large group of compounds. There is no suggestion in the art that would indicate that, provided the functional groups described in the specification or similar functional groups are present, the prodrug would definitely not be capable of functioning effectively in the presence of NQO2. Moreover, the number of possible CB 1954 analogs is small since there is only one real variant, i.e., the identity of R, in the analogs of the present application. Pharmaceutical patents are routinely granted covering millions of compounds with many different substituents being varied. The relevancy here is that the analogs of CB 1954 contain certain key functional groups that have been recognized and described in the specification at least a page 37, lines 22-26, as providing cytotoxicity following conversion by

NQO2. Therefore, there is predictability provided at least by the specification of the present application as to analogs which can be converted into cytotoxic drugs by the action of NQO2 based on the functional groups, such as the aziridine ring and nitro groups present in CB 1954 and analogs thereof, and the possible mechanism of action of NQO2 identified in Figure 1. Furthermore, Khan and Ross, *Chem. Biol. Interactions* 1 (1969/1970) pp. 27-47 ("Khan"), a copy of which is enclosed, referred to in the specification at page 37, lines 26-28 and also enclosed in the information disclosure statement mailed March 13, 2002 clearly indicate that a wide range of analogs of CB 1954 can have significant carcinostatic effectiveness provided that they contain an aziridine ring. Khan and Ross, *Chem. Biol. Interactions*, 4 (1971/1972) pp. 11-22 ("Khan 2"), a copy of which is enclosed, also referred to in the specification at page 37, lines 26-28, disclose analogs of CB 1954 that it would not be unreasonable to expect would work in the claimed system.

Methods for determining whether a substrate (i.e., the prodrug described in the present application) is converted by an enzyme (i.e. NQO2) are well known in the art. However, methods for testing whether a prodrug is converted by the action of NQO2 are disclosed in the specification at least at example 1, pages 55-57. Therefore, while some experimentation may be necessary to determine whether a prodrug is converted to a substantially cytotoxic drug by the action of NQO2, those of skill in the art routinely perform such experimentation as indicated in the specification of the present application, and the provided references Khan and Khan 2.

Furthermore, while no examples are necessary, the specification discloses at least at pages 73-76, examples of the effects of CB 1954 and NQO2 and co-substrates on the cytotoxicity of cells.

Therefore, based on the evidence provided above, the specification discloses to one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. Therefore, claims 34, and 41-45 are enabled by the specification.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 34, and 41-45 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 45 was also rejected under 35 U.S.C. § 112, second paragraph, as lacking sufficient antecedent basis from which this claim depends. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended. The rejection of claim 45 under 35 U.S.C. § 112, second paragraph, is moot since claim 45 has been canceled.

The Legal Standard

The second paragraph of 35 U.S.C. § 112 states that the claims must particularly point out and distinctly claim the subject matter regarded as the invention. The Applicant may use functional language, alternative expressions, negative limitations or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought (MPEP 2173.01). The MPEP further states that while the "Examiner is encouraged to suggest claim language to applicants to improve the clarity or precision of the language used" they "should not reject claims or insist of their own preferences if other modes of expression selected by applicants satisfy the statutory requirement" (MPEP 2173.02).

"Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore serves the notice function required by 35 U.S.C. 112, second paragraph. " (MPEP 2173.03 citing *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). As noted in the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

Claims 34, 41-44, and 46-47 are definite.

Claims 34, 41-44, and 46-47, as amended define a therapeutic system comprising a prodrug that is converted to a substantially cytotoxic drug by the action of NQO2 and a compound of formula I. The claims clearly define the term "therapeutic system" as a prodrug that is converted to a substantially cytotoxic drug by the action of NQO2 and a compound of formula I. Furthermore, the specification describes various types of therapeutic systems known by those of ordinary skill in the art in the specification at least at pages 1-3. Support for the use of the term "therapeutic system" as defined by the claims of the present application can be found

in the specification on page 37 lines 13-17, and again on page 38, lines 4-8. The specification and the claims clearly define the term "therapeutic system" as used in the present application. Therefore, one of ordinary skill in the art would be able to apprise the scope of the invention as defined by the claims. Therefore, the claims as amended are definite and meet the legal standard.

Allowance of claims 34, 41-44, and 46-47 is respectfully solicited.

Respectfully submitted,

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